Remarks

Claims 1-49 are pending. Claim 24 has been amended. Claims 1-23 are allowed. Claim 24 has been amended to clarify the sequences to be recombined. The clarified sequences correspond to those recombination sites of claim 1.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 24-49 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The specification does reasonably enable the use of a mutant Cre recombinase to produce site-specific recombination in a cell that has not been engineered to undergo site-specific recombination. The Examiner appears to have assumed that the sequence to be targeted for recombination in the cell is not the same sequence used in the methods to identify the recombinase. As stated at page 6 of the specification, "[T]he disclosed variant recombinases also allow recombination at *specific genomic sites* without the need to first introduce a recombination site" (see lines 22-23 of page 6). The methods involve producing mutant recombinases and testing the mutant recombinases with specially designed constructs. The constructs may contain variant recombination sites that are not recognized by non-mutant recombinase but will undergo recombination in the presence of a mutant recombinase with altered specificity. The sequences to be recombined in these specially designed constructs may be predicated on specific *genomic* sites.

Claims 24-49 are not reach through claims. The applicants were in possession of the claimed *methods* at the time of filing the present application. The term "reach through" claims is typically used when referring to patents that contain prophetic disclosures while claiming exclusive rights to all uses of the patented item. It would be possible to identify claim 24 as a reach through claim, *if* the variant recombinases were used in methods to identify heretofore unknown compounds, and the applicants were claiming the subject compounds having a *general* utility. The applicants are not claiming "downstream," or future, compositions that may be identified and isolated *via* the use of the variant recombinases already identified in claim 1. To the contrary, the applicants are claiming a method for using an *already identified* characteristic (known site-specific recombination) of the *already identified* variant recombinase in mediating recombination at sites that have *already been found* to be recombined per the method of claim 1. Any variant recombinase identified in the method of claim 1 is enabled for its use in claim 24. The identified recombinase has specific utility (recombining specific sites). These same sites have been introduced into claim 24.

Assertions as to one's ability to translate a mutation in one recombinase to a mutation in an entirely different recombinase (see page 8 of office action mailed on January 2, 2004), are completely unnecessary in view of the claimed screening methods wherein the variant recombinase is identified.

The claimed methods are not unpredictable. There is no need to identify mutations in recombinases that result in altered site-specificity. Applicants do not understand why the

examiner is making such "unpredictable" assertions when the recombinase identified in claim 1 is used to induce the ***same*** site-specific recombination in the DNA of claim 24.

Claims 24-49 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The claimed methods (claims 24-49) produce site-specific recombination of DNA. This recombination is accomplished by a method that comprises, *inter alia*, a) bringing into contact a mutant recombinase identified by the method of claim 1 with third and fourth DNA sequences, wherein the third DNA sequence comprises a fifth recombination site and the fourth DNA sequence comprises a sixth recombination site, wherein the variant recombinase mediates recombination between the fifth and sixth recombination sites thereby producing site specific recombination. The recombinase of claim 24 has *already* been established to mediate recombination at variant recombination sites. Claim 24 is a *method* claim for producing site-specific recombination. It is not a claim directed to a recombinase composition. It is not necessary for the present claims to specify the specific mutations that result in altered recombination site specificity. A representative number of mutant recombinases with altered recombination site specificity need not be disclosed with structural or functional features in order to provide proper support for a method claim.

The specification properly shows one how to identify an Int mutant, for example, that has altered recombination site specificity (the examiner agrees with this statement at page 5 of the

office action mailed on January 2, 2004). Once identified, the Int mutant is readily, and easily, isolated. The purpose of the method of claim 1 is to identify a variant recombinase, in order to make further use of its functional properties. To limit claims 24-49 to only the use of specifically characterized mutants would be unduly restrictive. The mutations in the enzymes of claims 24-49 need not be characterized in order to obtain desired sited-specific recombination. Claims 1-23 provide the researcher a clear avenue to pursue directed recombination.

The specification need not teach what is commonly known in the art. Page 14, lines 11-16, refer to references that identify and give explicit detail of the structure/function relationship for each of Beta recombinases, Int recombinases, and resolvases. The identification and characterization of the mutant Cre recombinase (Cre 262), shows that the claimed methods have in fact been reduced to practice. Furthermore, as evidenced by the references submitted with the response (mailed on July 9, 2003) to the office action mailed on April 9, 2003, several site-specific recombinases have already been shown to catalyze recombination in multicellular organisms after a first demonstration that they catalyze recombination in cultured cells. For example, Cre in mice (Lakso *et al.*, *Proc. Natl. Acad. Sci. USA* 89:6232-6236; *Methods* 14:381; *Curr. Opin. Biotechnol.* 10:470); Cre in plants (Odell *et al.*, U.S. Patent No. 5,658,772); Flp in mice (Dymecki, S., 1996, *Proc. Natl. Acad. Sci. USA* 93:6191; phiC31 Int in mice (Olivares *et al.*, 2002, *Nat. Biotechnol.* 20:1124).

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AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 24-49 is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, March 26, 2004, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Peggy Bailey

Date: March 26, 2004

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